# Novel *FLNB* Variants in Seven Argentinian Cases with Spondylocarpotarsal Synostosis Syndrome

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## Abstract

Spondylocarpotarsal synostosis syndrome (SCT) is a very rare skeletal dysplasia characterized by vertebral, carpal, and tarsal fusion; growth retardation; and mild dysmorphic facial features. Variants in *FLNB, MYH3,* and *RFLNA* have been implicated in this dysplasia. We report the clinical and radiological follow-up of seven SCT pediatric cases associated with biallelic *FLNB* variants, from four Argentinian families. The seven cases share previously described facial characteristics: round facies, large eyes, and wide based nose; all of them had variable height deficit, in one case noted early in life. Other findings included clinodactyly, joint limitation without bone fusion, neurosensorial hearing loss, and ophthalmological compromise. All cases presented with spinal fusion with variable severity and location, carpal bones coalition, and also delay in carpal ossification. The heterozygous carrier parents had normal height values to −2.5 score standard deviation, without skeletal defects detected. Three different *FLNB* variants, one nonsense and two frameshift, were detected, all of which were predicted to result in a truncated protein or are degraded by nonsense mediated decay. All cases had at least one copy of the nonsense variant, c.1128C> G; p. (Tyr376*), suggesting the presence of a common ancestor.

**Keywords**
- spondylocarpotarsal synostosis syndrome
- filamin B
- carpal coalition
- scoliosis
- skeletal dysplasia

## Introduction

Spondylocarpotarsal synostosis syndrome (SCT, MIM 272460) is a very rare skeletal dysplasia (SD). It is characterized by vertebral fusions causing spinal deformity and growth retardation, fusion of carpal and tarsal bones, and mild dysmorphic facial features including round face, frontal bossing, ocular hypertelorism, and anteverted nostrils.[1–3] Variants in *FLNB, MYH3, and RFLNA* genes have been implicated in this condition.[4–7]

Biallelic variants in the filamin B gene (*FLNB*), located on chromosome 3p14.3, cause loss of function of cytoplasmic protein filamin B.[4,6,8,9] *FLNB* is expressed in chondrocytes in the growth plate, and in developing vertebral bodies. It has a central role in skeletal morphogenesis, endochondral ossification, vertebral segmentation, and joint formation by

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regulating intracellular communication and signaling by cross-linking actin and, thus, providing a scaffold to connect the cell membrane to the cytoskeleton.[6,8,10–12] Apart from SCT, *FLNB* pathogenic variants also cause various other skeletal disorders; Boomerang dysplasia (MIM 112310), Larsen syndrome (MIM 150250), and atelosteogenesis I/III (MIM 108720, 108721), which are also characterized by disrupted vertebral segmentation, joint formation, and endochondral ossification.

Other causative gene, *MYH3*, encoding the myosin 3 heavy chain, has been identified in families with dominant and recessive SCT, and SCT associated with multiple pterygium syndrome.[5,13–16] Variants in this gene have also been associated with a group of autosomal dominant distal arthrogryposis, type 2A and 2B (MIM 193700, 601680), and multiple pterygium syndrome (MIM 178110). More recently, a homozygous frameshift variant in *RFLNA* gene has been identified in a patient with typical features of SCT.[7]

In SCT, prenatal growth is normal but subsequent growth retardation and short trunk occur due to progressive vertebral fusion. The height deficit is variable, varying between −3 and −6 score standard deviation (SSD).[1,3] In clinical presentation, scoliosis is a common sign but is variable in severity and time of onset, usually becoming evident late in childhood. Other features include cleft palate, conductive, sensorineural or mixed hearing loss, clubfoot, retinal abnormalities, joint hypermobility, tooth enamel hypoplasia, restrictive lung disease, kidney cysts, and urolithiasis..[1,2,17–21] Intelligence is normal in these cases. In cases with *MYH3* variants, variable contractures of the neck, shoulders, elbows, fingers, hips or knees, camptodactyly, clinodactyly of the 5th finger, and basilar invagination has also been described.[5,13–15]

Radiological signs of SCT include the (1) fusion of adjacent vertebrae and posterior elements involving contiguous and noncontiguous areas of the spine. Asymmetric fusion of posterior elements results in the formation of unilateral bars,[1] fusion of pedicles in the midline has also been described,[22] as cervical instability.[23,24] (2) Synostosis of the tarsal and carpal bones, more frequently between the capitate and hamate, and between the lunate and the triquetrum. (3) Delayed ossification of the epiphyses and delayed bone age. (4) Bilateral femoral dysplasia, rib abnormalities, and platybasia with basilar invagination.[2,25–27]

In this study, we report the detailed clinical and radiological follow-up of seven cases with SCT from four families, in whom biallelic *FLNB* variants were detected. These cases were evaluated at the SD multidisciplinary clinic at Garrahan Pediatric Hospital, Argentina.

## Clinical Reports

Clinical cases are summarized in ►**Table 1**, along with previously described cases.

*Cases 1, 2, 3 (Family 1)*: Three sisters from a family of five children, born to healthy consanguineous couple, were referred for short stature and scoliosis, at the ages of 10.2, 5.8, and 4.8 years. Perinatal history was unremarkable and birth length (BL) and birth weight (BW) were in the normal range for all three siblings (BW: −0.33, 0.55, −0.38 SSD, BL: NA, 0.62, 0.22 SSD; and cranial circumference [CC]: NA, 0.84, −1.29 SSD), respectively. They have mild facial dysmorphisms in the form of round facies, large eyes, and broad-based nose and also bilateral 5th finger clinodactyly. They did not have any serious health events, no neurological compromises, and abdominal and renal ultrasounds were within normal limits. Development and schooling are also normal. Case 2 required scoliosis correction surgery (instrumented posterior arthrodesis T3-L2) at the age of 10.1 years. Anthropometric details[28–30] are shown in ►**Fig. 1A–E**. Hand radiographs of the three sisters showed capitate-hamate coalition, delayed carpal ossification, and clinodactyly of the 5th fingers and the older one also had lunate-triquetrum coalition (►**Fig. 2A–C**). Spine radiographs show coalition of posterior elements of the spine (►**Fig. 3A–F**). Feet radiographs of case 2 showed no tarsal coalition at 5.8 years.

*Cases 4, 5 (FAMILY 2)*: Two brothers from a family of three children were born to a healthy, apparently nonconsanguineous couple. They came to the clinic at the ages of 9.8 and 6.4 years, respectively, due to short stature and scoliosis. In addition, case 4 also presented with congenital unilateral palpebral ptosis. They did not have any significant perinatological events and birth anthropometry data was normal (BW: −0.31, −1.11 SSD, BL: −1.21, −1.75 SSD, CC: 0.85, 0.17 SSD). They presented with mild facial dysmorphisms in the form of round facies, large eyes, and broad-based nose. Both have no other illnesses, no neurological compromise, and other evaluations including abdominal and renal ultrasounds, audiological and ophthalmological evaluations, and functional respiratory examinations were normal. They had learning difficulties but attended normal school. Height, sitting height, leg length, and body proportions during the follow-up are shown in ►**Fig. 4A–E**. Skeletal radiographs of hands revealed carpal coalition (capitate-hamate), with delayed carpal ossification (►**Fig. 2D–E**), and coalition of posterior elements in the vertebral column (►**Fig. 3 G–K**). Foot radiographs were not performed.

*Case 6*: A 1.5-year-old boy with short stature (−3.0 SSD) was referred for endocrinological evaluation. Perinatal or family history data was not available for this case. Renal and abdominal ultrasounds and echocardiogram were within normal limits. At the age of 4.7 years, a malformation was detected in the dorsal spine, and at 6.9 years of age small hands and fusion of the carpal bones were noticed. He had a short and wide nose, and limitation of elbow and finger extension in both hands. In the follow-up, he presented with unilateral neurosensorial hearing loss, myopia, and astigmatism that required correction. He required adenotonsillectomy surgery for snoring. Height, sitting height, leg length, and body proportions during the follow-up are shown in ►**Fig. 4A–E**. The skeletal findings are similar to those described in cases 1 to 5 (►**Figs. 2F–G**, **3L–M**). Early age hand radiograph shows overlapping carpal bones and brachy metacarpals, especially of the first metacarpal. No tarsal coalition was observed at 11.7 years.

 

**Table 1** Summary of cases along with previously described ones

| | Cases 1–3 | Cases 4–5 | Case 6 | Case 7 | Summary | Yasin et al 2021[35] | Salian et al 2018[3] | Yang et al 2017[27] | Brunetti-Pierri et al 2008[25] | Mitter et al 2008[2] | Krakow et al 2004[6] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of cases/ families** | 3/1 | 2/1 | 1/1 | 1/1 | 7/4 | 5/1 | 10/7 | 2/1 | 1/1 | 1/1 | NA/4 |
| **Causes for referral** | | | | | | | | | | | |
| Short stature | 3/3 | 2/2 | 1/1 (1.5 yo) | 0/1 | 6/7 | NA | NA | NA | 1/1 | 1/1 | NA |
| Scoliosis | 3/3 | 2/2 | 0/1 | 1/1 (3 mth) | 6/7 | NA | NA | NA | 1/1 | 1/1 | NA |
| **Age at 1st consultation (yo)** | 10.2, 5.8, 4.8 | 9.8, 6.4 | 1.47 | 5.97 | Median 5.97 | Range: 7.0–32.0 | Range: 0.6–15.0 | 24.0, 26.0 | 3.0 | 5.6 | NA |
| **Facial dysmorphism** | | | | | | | | | | | |
| Facies | Round 3/3 | Round 2/2 | Round 1/1 | Round 1/1 | Round 7/7 | Mild frontal bossing 3/5 | Mild coarse face, frontal bossing 2/10 | NA | Non dismorphic 1/1 | Frontal bossing 1/1 | Craniofacial abnormalities 2/4 families |
| Eyes | Large 3/3 | Large 2/2 | Large 1/1 | Large 1/1 | Large 7/7 | NA | NA | NA | NA | NA | NA |
| Nose | Broad based 3/3 | Broad based 2/2 | Broad based 1/1 | Broad based 1/1 | Broad based 7/7 | Anteverted nostrils 3/5 | NA | NA | NA | Anteverted nostrils 1/1 | NA |
| **Size at birth (median—SSD)** | Normal | Normal | NA | Normal | Normal 6/6 (W: −0.36, L: −1.21, CC: 0.84) | NA | NA | NA | Normal | Normal | NA |
| **Short stature (SSD)** | 3/3 (−4.14, −3.12, −3.37) | 2/2 (−4.05, −2.86) | 1/1 (−3.03) | 1/1 (−2.88) | 7/7 (median: −3.12) | 5/5 (range: −5.1-(−) 3.4) | 10/10 (range: −9.5-(−) 2.4) | 2/2 (NA) | 1/1 (−3.6) | 1/1 (−4.0) | NA (NA) |
| **Radiology** | | | | | | | | | | | |
| **Hands** | | | | | | | | | | | |
| Carpal fusion | Capitate–hamate 3/3 Lunate–triquetrum 1/3 | Capitate–hamate 2/2 Lunate–triquetrum 0/2 | Capitate–hamate 1/1 Lunate–triquetrum 1/1 | Capitate–hamate 1/1 Lunate–triquetrum 0/1 | Capitate–hamate 7/7 Lunate–triquetrum 2/7 | Capitate–hamate 5/5 | Capitate–hamate 9/10 Lunate–triquetrum 3/10 | Capitate–hamate 2/2 | Capitate–hamate 1/1 | Capitate–hamate 1/1 | Carpal anomalies 4/4 families |
| Delayed carpal ossification | 3/3 | 2/2 | 1/1 | 0/1 | 6/7 | NA | NA | NA | 1/1 | 1/1 | NA |
| **Feet** | | | | | | | | | | | |
| Tarsal coalition | 0/1 (5.8 yo) | NA | 0/1 (11.7 yo) | 0/1 (5.6 yo) | 0/3 | 1/5 | 5/10 | 0/2 | 0/1 | NA | Tarsal anomalies 1/4 families |
| **Spine** | | | | | | | | | | | |
| Fusion | 3/3 | 2/2 | 1/1 | 1/1 | 7/7 | 5/5 | 10/10 | 2/2 | 1/1 | 1/1 | 3/4 families |
| **Family analysis** | | | | | | | | | | | |
| **Genetic analysis** | NA | Heterozygous carriers | NA | Heterozygous carriers | Heterozygous carriers (2 families) | Heterozygous carriers | NA | NA | Heterozygous carriers | Heterozygous carriers | NA |
| **Parents height SSD** | −1.66, −1.56 | −2.5, −0.65 | NA | −0.13 | Median −1.56 | 1/7–1.8 | NA | NA | −1.6, −2.0 | 0, −2.2. | NA |
| **Parents Rx** | No carpal fusion. | NA | NA | No carpal or vertebral fusion. | 4/4 no carpal fusion. 2/2 no vertebral fusion | NA | NA | NA | NA | Unilateral hip dysplasia | NA |

Abbreviations: CC, cranial circumference; F, female; L, length; M, male; mth, month; *n*, number; NA, not available; SSD, score standard deviation; W, weight; yo, years old.

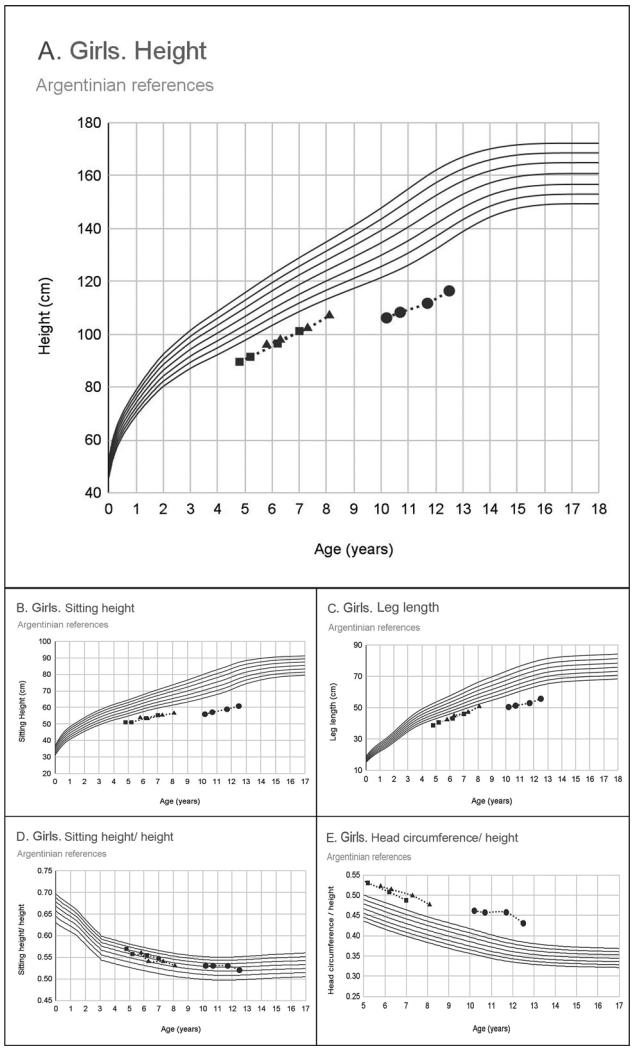


**Fig. 1** (**A–E**) Height, sitting height, leg length, sitting height/height, head circumference/ height of Argentinian girls. Girls of family 1 had a moderate-to-severe deficit in height (−4.7, −3.3, and −3.5 score standard deviation) at the first visit, with compromise of the trunk height and the lower limbs length, without body disproportion assessed as sitting height/ height ratio but relative macrocephaly.

*Case 7*: The sixth child of a healthy, non consanguineous couple, was referred at 6 yo for scoliosis detected at 3 months of age, which required posterior lumbar and thoracic arthrodesis at the age of 11.4. He had no perinatal events and was born with a normal size for gestational age (BW: −0.48 SSD, BL: −1.57 SSD, CC: 1.14 SSD). He presented with mild facial dysmorphisms as flat facies and large eyes. He was hospitalized at 3 months of age for bronchiolitis, without requiring respiratory assistance, and had a left hip Perthes disease at 5 years of age. He has no neurological compromise and organ studies including abdominal and renal ultrasound, audiological and ophthalmological evaluation were normal. Schooling was normal. Height, sitting height, leg length, and body proportions are shown in ►**Fig. 4A–E**. Radiology is shown in ►**Fig. 2H** and **3N–O**. No tarsal coalition was found at 5.6 years.

The parents of cases 4, 5, and 7 were heterozygous carriers of the variants and had height between normal to −2.5 SSD, compared with local population. Hands and spine radiographs, if available, were within normal limits.

## Genetic Studies

Ethical considerations: Study approval was obtained from local ethical committees and all participants provided informed consent for the performed studies. Blood samples were extracted from the cases and parents when possible. We studied known genes and regions implicated in SD using the custom designed next-generation sequencing SD panel that included 368 genes and data was generated using Illumina NextSeq platform, as described previously.[31] Variants of interest and cosegregation analysis were confirmed by Sanger sequencing.

The molecular genetic results are shown in ►**Table 2**. Two of the families (families 1 and 3) had the same homozygous nonsense variant, while the other two families, families 2 and 4, had compound heterozygous variants, one of which was the same nonsense variant as that detected in families 1 and 3 and other two frameshift variants were different. All the variants were predicted to generate a truncated protein or were predicted to be degraded by nonsense mediated decay. They were not reported in population databases such as gnomAD or variant databases such as ClinVar, LOVD, HGMD and were classified as pathogenic variants according to the recommendations by the American College of Medical Genetics and Genomics guidelines.[32]

## Discussion

Filamins (*FLNA, FLNB, FLNC*) belong to the family of actin-binding proteins, having a central role in spatiotemporal cytoskeletal dynamics as mechanotransduction elements. This process is essential for cellular motility and differentiation. Mutations in *FLNB* gene, expressed in chondrocytes in the growth plate and in developing vertebral bodies, are associated with two groups of chondrodysplasias. Homozygosity or compound heterozygosity for null alleles causing upregulation of TGF-β signaling results in SCT, while heterozygosity for missense mutations or small in-frame deletions results in boomerang dysplasia, Larsen syndrome, and atelosteogenesis I/ III.[6,8,10–12,33] Refilin-A (*RFLNA*) and Refilin-B (*RFLNB*) are vertebrate-specific filamin-binding proteins, downstream effectors of TGF-β signaling, and suggested to regulate the mechanosensory functions of filamin during skeletal development.[34] A homozygous frameshift variant in Refilin-A (*RFLNA)* has been identified in a patient with typical features of SCT, providing evidence of the functioning of the *FLN- RFLN* complex.[7]

SCT caused by pathogenic *FLNB* variants are rare findings and only a few of these patients have had molecular confirmation, with the largest series reported data for seven families.[3] In this study, three different *FLNB* variants, one nonsense and two frameshift, were detected in the four families, all of which are predicted to result in a truncated

 

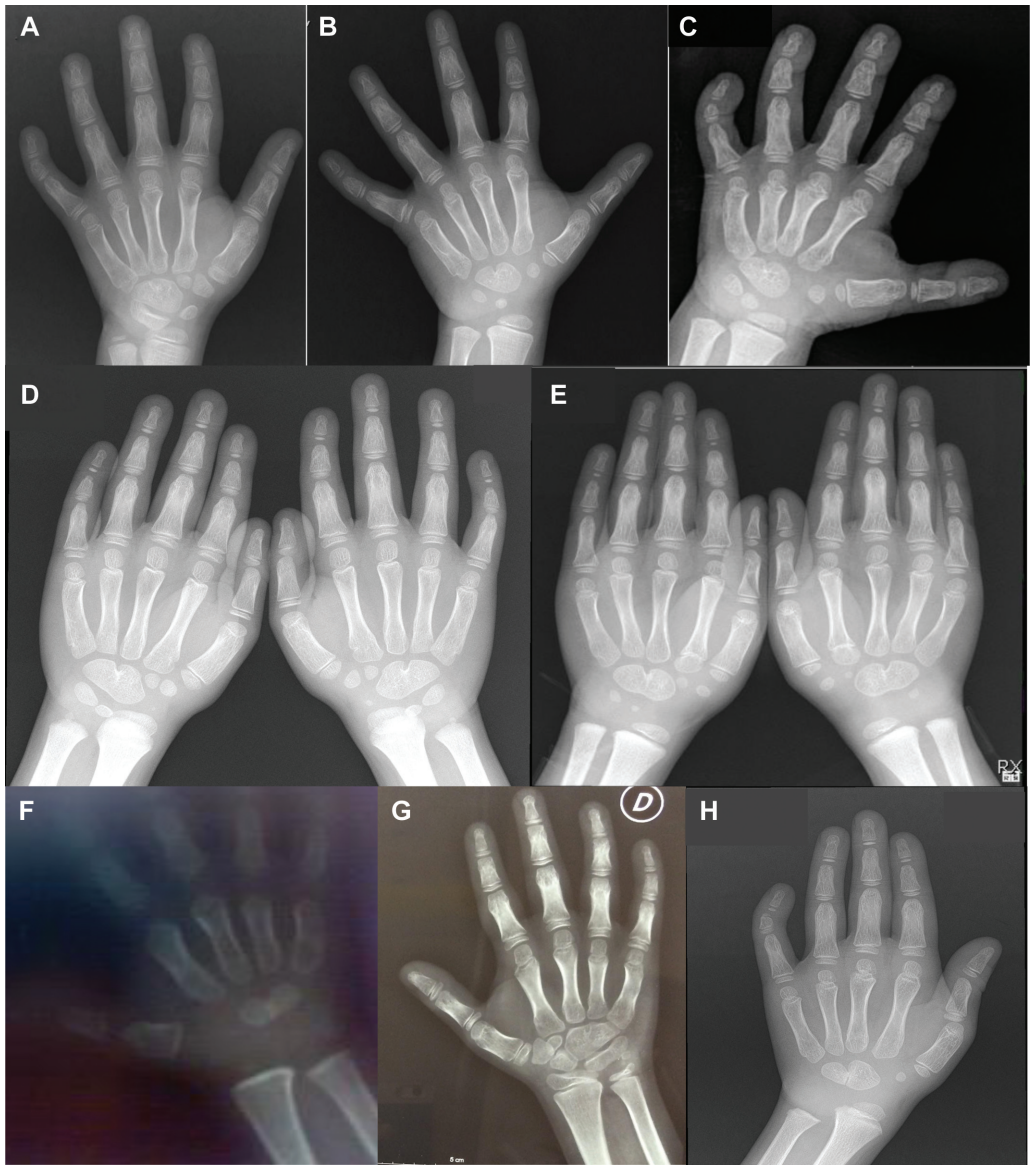


**Fig. 2** (**A–C**) Cases 1 to 3, girls, at 10.2, 5.8, and 4.8 years. Coalition of carpal (capitate-hamate in all, in the older one, lunate -triquetrum) bones with delayed carpal ossification. Clinodactyly of the 5th fingers. (**D–E**) Cases 4 and 5, boys, at 10.5 and 6.5 years. Coalition of carpal (capitate-hamate) bones, with delayed carpal ossification. (**F–G**) Case 6, at first appointment and at 11.7 years. Short metacarpals, especially the 1st one. Incipient carpal coalition at early age, evident at 11.7 years (capitate-hamate and lunate-triquetrum). (**H**) Case 7, at 5.6 years. Coalition of carpal (capitate-hamate) bones with delayed carpal ossification. Clinodactyly of the 5th finger.

protein or degraded by nonsense mediated decay. Interestingly, all cases had at least one copy of the nonsense variant, c.1128C> G; p. (Tyr376*). Although no haplotype analysis was performed, the presence of common nonsense variant p. (Tyr376*) in all cases likely suggests a common ancestor for families' studies.

Here, we describe the clinical, radiological, and genetic characteristics of seven cases from four Argentinian families. The patients in our study share facial characteristics previously described in SCT patients such as round facies, large eyes, and wide based nose. However, none of our cases had cleft palate that has been described in SCT cases. Three sisters in family 1 had clinodactyly of the 5th finger in both hands. Case 6 had joint limitation of elbows and fingers without bone fusion. He also had neurosensorial hearing loss as previously described[1,18]; and ophthalmological compromise, although he did not have cataracts or retinal abnormalities as previously reported.[21]

All of our cases had variable height deficit. In case 6, the height deficit was noted early in life, this was described in one previous case[2], contrary to most reports where height deficit appears later in life.[2,19,25,35] In all cases, the short stature was not only due to the compromise of the trunk but also due to shorter legs. This has also been observed in the *FLNB*-deficient mice.[10]

All cases presented with spinal fusion and carpal bones coalition. Spinal fusion was variable in terms of severity (two children required arthrodesis surgery) and location, although in all cases there was compromise of contiguous dorsal vertebrae. In case 7, the spinal issues involved

 

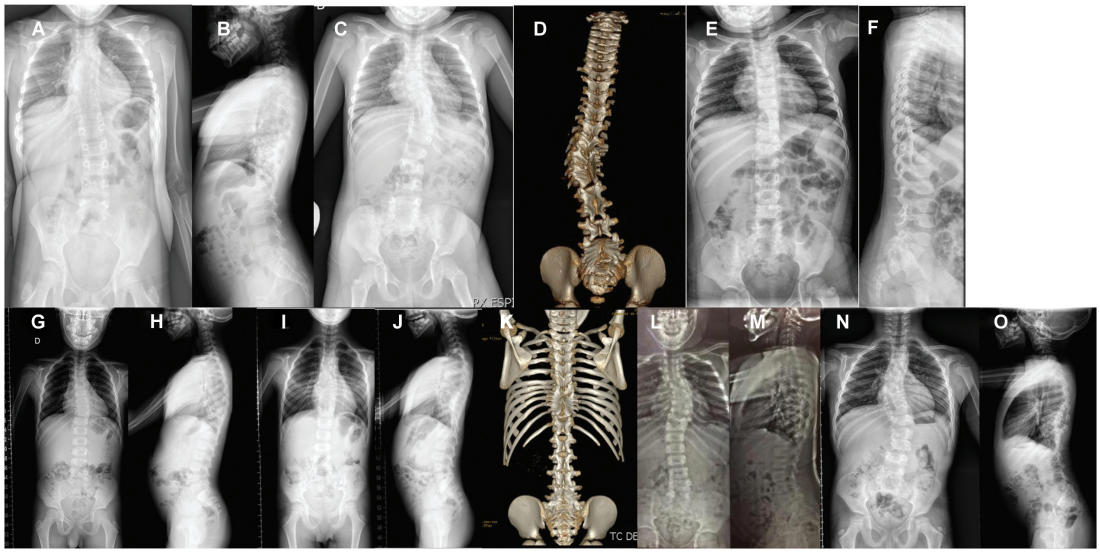


**Fig. 3** (**A–F**) Cases 1 to 3. (**A, B**). Case 1 at 10.2 years. (**C, D**). Case 2 at 5.8 and 7.0 years (computed tomography [CT]). (**E–F**). Case 3 at 4.8 years. (**G–K**) Cases 4 and 5 (G–H). Case 4 at 10.5 years. (**I–K**) Case 5 at 6.5 and at 7.8 years (CT). (**L–M**) Case 6 at 11.7 years. (**N–O**) Case 7 at 5.6 years. The pictures show coalition of posterior elements of the spine, at different levels.

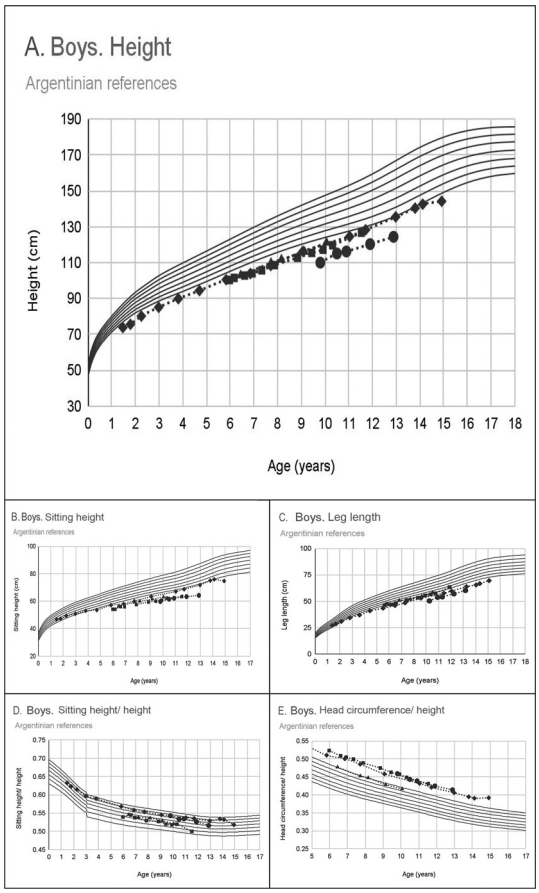


**Fig. 4** (**AE**) Height, sitting height, leg length, sitting height/ height, head circumference/height of Argentinian boys. Boys affected had moderate-to-severe deficits in height (between −2.86 and −4.05 score standard deviation [SSD]) at the first visit, with compromise of the trunk height and the lower limbs length, without body disproportion assessed as sitting height/height ratio, but relative macrocephaly. Case 6 (diamond dots) started the follow-up at 1.5 years with height deficit −3.0 SSD, growth was normal, height deficit at last visit at 14.9 years was −2.4 SSD.

early onset scoliosis already present at 3 months of age. None of them had atlantoaxial instability as described in other cases.[24] The fusion of the carpal bones, as described in the literature, was between the capitate and hamate bones in all, and in the older cases, fusion between the lunate and the triquetrum bones was evidenced, probably due to the evolutionary nature of the condition. The carpal bones were small and irregular, and there was also a delay in carpal ossification, described by other authors.[26] In cases 2, 7, and 6, where feet radiographs were available, fusion of the tarsal bones was not observed at 5.8, 5.6, and 11.7 years, respectively. The child in case 7 had unilateral Perthes disease without sequelae, but we have not seen femoral head dysplasia, as described in previous cases.[2]

The heterozygous carrier parents had variable height SSD, from normal values to −2.5 SSD. No radiographic skeletal defects were detected. Other reported cases have shown a similar height deficit in heterozygous cases but one case was reported to have had hip dysplasia.[2]

## Conclusion

SCT is a rare condition, caused by pathogenic variants in *FLNB, MYH3,* or *RFLN* gene. We describe seven Argentinian cases associated with biallelic *FLNB* variants resulting in loss of protein functions. All the cases shared at least one copy of the nonsense variant, p.(Tyr376*), suggesting the presence of a common ancestor. The seven cases presented spinal fusion with scoliosis, and carpal bones coalition. In one case, the involvement of the spine was detected early in life. All of our cases had variable height deficit with involvement of the trunk and length of the lower limbs. Their heterozygous carrier parents appeared to have mild height compromise.

 

**Table 2** FLNB genetic variants detected in cases 1–7 (four families). The variant present in all individuals is shown in bold

| Case number (family) | Variant(s) cDNA* | Exon(s) | Variant(s) amino acid |
|---|---|---|---|
| 1–3 (family 1) | **c.[1128C > G];[1128C > G]** | 7 | **p.[(Tyr376*)];[(Tyr376*)]** |
| 4–5 (family 2) | **c.[1128C > G]**;[2911dup] | 7, 20 | **p.[(Tyr376*)]**;[(Ala971Glyfs*122)] |
| 6 (family 3) | c.**[1128C > G];[1128C > G]** | 7 | **p.[(Tyr376*)];[(Tyr376*)]** |
| 7 (family 4) | c.[992dup];**[1128C > G]** | 7, 7 | p.[(Leu332Profs*13)];**[(Tyr376*)]** |

*NM_001457.4.

Ethical Approval

This is an observational study. Study approval was obtained from local ethical committees.

Patient Consent

All participants provided informed consent for the performed studies.

Authors' Contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Ramos-Mejia Rosario, del Pino Mariana, Abbate Silvina, Obregon M.Gabriela, and Fano Virginia. Genetic studies were performed by Heath Karen E. and Aza-carmona Miriam. The first draft of the manuscript was written by Ramos-Mejia Rosario, and all authors commented on previous versions of the manuscript. All authors revised the manuscript critically and approved the final version. All of them agree to be accountable for all aspects of the work.

Conflict of Interest

None declared.

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